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Favorable Outcome After 1-Year Treatment of Childhood T-Cell Lymphoma/T-Cell Acute Lymphoblastic Leukemia

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Background. For T-malignancies in children a poor prognosis is reported. In these malignancies a combination of lymphoma and leukemia is commonly seen at presentation and most patients are treated according to protocols for acute lymphoblastic leukemia (ALL). These protocols are often designed for the majority of ALL cases, i.e., progenitor-B-ALL. In pediatric lymphoblastic non-Hodgkin's lymphoma without bone marrow infiltration various protocols have been used. The most frequently reported regimens show variable survival rates between 40 and 75%.

Patients and Methods. From 1989 we have treated 32 consecutive patients with T-cell malignancies, irrespective of localization, with a protocol consisting of a 4-agent induction treatment followed by high doses of methotrexate, and cytosine-arabinoside and intensified bleomycin, adriamycin, cyclophosphamide, vincristin, prednisone (BACOP) courses. Treatment duration for each patient was 1 year. Twenty-one of the 32 patients had stage IV disease. Follow-up ranged from 1.6 to 7.6 years (median 4.2 years).

Results. Overall event-free survival (EFS) was 72%, while in those with stage IV disease it was 67%. No therapy-related deaths occurred. Neither stage, initial leukocyte value, mediastinal involvement, bone marrow involvement, nor the presence of CD1, CD3, CD4, CD8, or CD10 epitopes was prognostically significant. Evaluation of toxicity revealed a minimal decrease of carbon monoxide diffusion and cardiac shortening fraction.

Conclusion. A relatively short but intensive chemotherapy can be used in T-cell malignancies. The EFS is satisfying, but larger studies are needed. Med. Pediatr. Oncol. 30:46–51, 1998.

Key words: T-cell; leukemia; lymphoma; chemotherapy; pulmonary function; cardiac function

INTRODUCTION

About 15% of children with lymphoblastic disease have a T-cell malignancy [1,2]. Features of these children are older age, higher leukocyte counts, the presence of a mediastinal mass, central nervous system (CNS) infiltration and a worse prognosis, compared with non-T-lymphoblastic malignancies [2–5]. Currently, most groups treat T-cell malignancies in children with standard protocols. The most widely used specific protocol is the LSA_2-L_2 scheme; the French LMT81-regimen is derived from it [6–8].

It is difficult to distinquish T-cell acute lymphoblastic leukemia (T-ALL) from stage IV T-cell lymphoma, due to the high percentage of lymph node involvement and mediastinal enlargement in T-ALL. Instead of localization, other characteristics, such as length of the cell cycle and drug sensitivity, might be more essential factors to be taken into consideration when planning treatment. Here we report the results of a 1-year regimen of multidrug chemotherapy in 32 consecutive patients with T-cell non-Hodgkin's lymphoma (T-NHL)/T-ALL.

PATIENTS AND METHODS

From September 1989 until October 1995, 32 consecutively diagnosed children and adolescents (<18 years) suffering from T-NHL/T-ALL have been included in the study. Pretreatment evaluation included a detailed patient history, physical examination, bone marrow aspiration (cytomorphology, immunology, cytogenetics), examination of spinal fluid (cytomorphology, immunology, cell count), complete blood count, urine examination, liver and kidney function tests, serum uric acid, chest X-ray, and abdominal ultrasound examination. Biopsies of an involved lymph node for pathological examination, cytology, immunology, and cytogenetics were done in those cases where the bone marrow examination was inconclusive. Immunology was carried out on bone marrow aspirates, cerebrospinal fluid, and cytologic material from lymph nodes using stardard monoclonal antibodies

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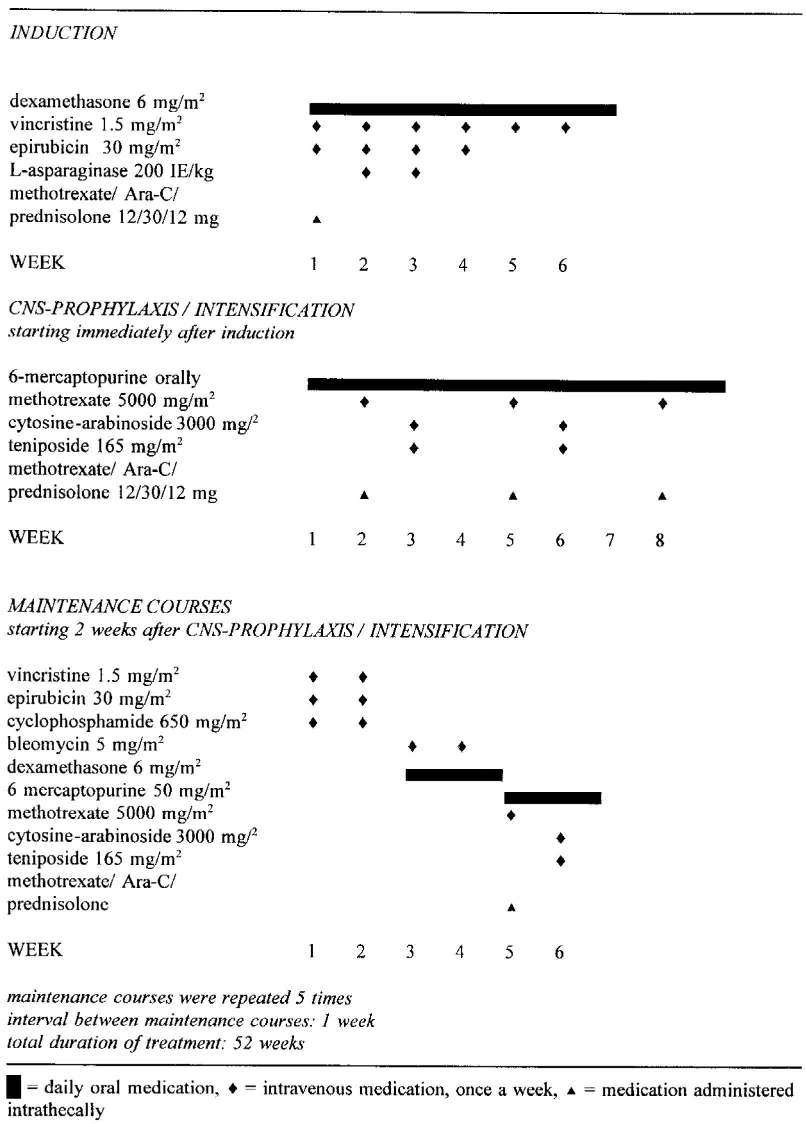

Fig. 1. Chemotherapy regimen for children with T-cell malignancies.

(directed against CD1, CD2, CD3, CD4, CD7, CD8, CD9, CD10, CD11c, CD13, CD14, CD15, CD16, CD19, CD20, CD24, CD25, CD33, CD34, CD56, HLA-DR, and glycophorin A as determined by flow cytometry using a FACSstar; and anti-TdT and cytoplasmic-IgM and -CD3 as determined by immunocytology); positivity was defined as >20% of the blasts. Histologic examination was performed using standard techniques for immunohistochemistry. Staging of the lymphoma was done according to the Murphy [9] classification. Leukemic infiltration of the bone marrow was defined as >50 acid phosphatase positive lymphoblasts counted in 200 bone marrow nuclear cells. For toxicity survey during treatment, pulmonary carbon monoxide diffusion (COD) was measured prior to every modified bleomycin, adriamycin, cyclophosphamide, vincristin, prednisone (BACOP) course and at completion of therapy. Obtained values were corrected for hemoglobin, height, and weight, and compared with healthy controls. Ultrasound examination of the heart and determination of the left ventricle shortening fraction was done prior to adriamycin, after 200 mg/m^2, and after every further 60 mg/m^2 administration.

After obtaining informed consent all patients were treated according to the protocol outlined in Figure 1, irrespective of the stage of the disease. At the end of treatment the cumulative dose of epirubicin was 420 mg/m^2, of bleomycin 50 mg/m^2, and of cyclophosphamide 6,500 mg/m^2. Patients with involvement of the CNS also received cerebrospinal irradiation.

Statistical Analysis

For analysis of differences in survival according to stage, initial leukocyte values, and immunological markers, a Cox-Mantel log rank and a generalized Wilcoxon

(Breslow) test were applied. Kaplan-Meier curves were obtained for event-free survival (EFS). For differences between shortening fraction (as determined on echocardiography) and COD at the start and at the end of treatment, the Wilcoxon matched-pair signed-ranks test was applied.

RESULTS

Thirty-two patients were treated with the outlined protocol (18 males and 14 females). Ages at diagnosis were between 0.6 and 17.8 years (median 9.5 years). Localizations at diagnosis were: mediastinum (21 patients), lymph nodes above the diaphragm (mediastinal localizations excluded; 15 patients), pleural (2 patients), pharynx (1 patient), lymph nodes below the diaphragm (5 patients), CNS (5 patients), bone marrow (19 patients; 2 had <25% blasts). One patient was classified as stage I, 10 patients as stage III, and 21 patients as stage IV. Leukocyte counts ranged between 3.9 and 890 × 10^9/l (median 51 × 10^9/l). Patients with bone marrow involvement had values between 7.6 and 890 × 10^9/l (median 89 × 10^9/l); those without bone marrow involvement had values between 3.9 and 11.9 × 10^9/l (median 10.2 × 10^9/l).

Data on immunophenotyping of malignant cells from bone marrow and/or a lymph node suspension as determined by FACS analysis were available in 31 patients (data are given in Table I). Cytogenetic results were available on 26 patients. In 18 patients chromosomal abnormalties were found. These included three translocations, two of which are known to be associated with T-ALL/lymphoma, i.e., t(10;14)(q24;q11) (2 patients) and t(11;14)(13;q11) (1 patient); 1 patient had t(7;9)(q31;q34). The majority of patients had deletions of the long arm of chromosome 6 and/or structural variation involving the short arms of chromosomes 9 and 12 and the long arm of chromosome 13 which are known to be associated with childhood ALL in general [10].

Outcome

The follow-up period ranged from 1.6 to 7.6 years from diagnosis, with a median 4.2 years. Nine children developed a relapse; 6 of them had bone marrow involvement at initial diagnosis. Four relapses occurred during treatment; the others were noted 15, 16, 17, 18, and 18 months after diagnosis. The relapse sites were as follows: CNS (5 patients; 1 of these patients had initial CNS involvement), mediastinal lymphoma (4 patients), bone marrow (1 patient), and testicular (isolated) relapse (1 patient). All patients experiencing a relapse ultimately died from treatment-resistant disease. Overall EFS was 72% (Fig. 2). The relation between clinical features at diagnosis and outcome is shown in Table I. None of the tested parameters reached significance. There were no toxic deaths.

TABLE I. Outcome in Relation to Presenting Features

Factor	EFS (%)	*P*
Overall	72	
Stage		
I (n = 1)	100	0.70
III (n = 10)	80	
IV (n = 21)	67	
Mediastinal involvement		
Present (n = 11)	81	0.28
Absent (n = 21)	66	
Bone marrow involvement[a]		
Yes (n = 19)	76	0.59
No (n = 13)	68	
CD1[b]		
Negative (n = 13)	61	0.32
Positive (n = 18)	77	
CD3 (surface)[b]		
Negative (n = 10)	80	0.45
Positive (n = 21)	66	
CD4[b]		
Negative (n = 11)	81	0.38
Positive (n = 20)	65	
CD8[b]		
Negative (n = 15)	80	0.35
Positive (n = 16)	63	
CD10		
Negative (n = 23)	65	0.19
Positive (n = 8)	87	

[a]As determined by standard morphology.
[b]Data of one patient are lacking, as only data obtained by FACS analysis were considered.

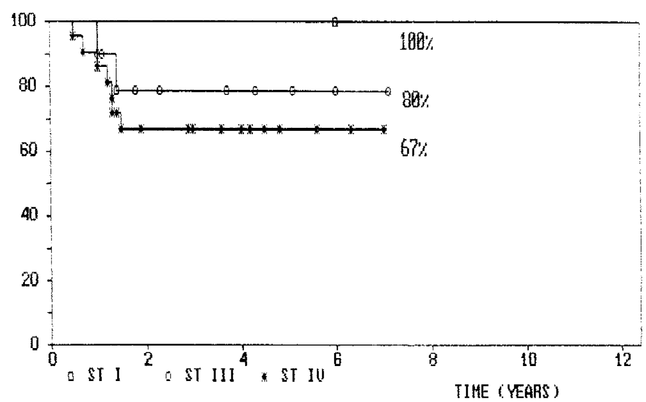

Fig. 2. Event-free survival according to stage.

Toxicity

Myelosuppression was the most frequently encountered sign of toxicity during induction and during further treatment. Incidentally, this resulted in extension of treatment duration up to 2 months. In the majority of patients chemotherapy-related stomatitis was observed.

In all children data on the left ventricle shortening fraction (LVF) could be evaluated. Prior to anthracycline

therapy LVF ranged from 31 to 51% (median 40%). At the end of treatment LVF ranged from 29 to 47% (median 37%). In 27 children comparison of LVF data prior to and after cessation of therapy was possible. In a statistically significant number of children (n = 19; $P < 0.01$) a slight decrease in shortening fraction (range 2–14%, median 5%) was noted. Clinically 1 patient showed left ventricular failure; presently, while still receiving digoxin medication, she is actively participating at a normal level in her sportclub with a shortening fraction of 30%.

Concerning bleomycin toxicity, 25 patients were tested by determination of COD. In the remaing 7 children this was not possible due to age and/or mental state. Prior to the first bleomycin administration, COD values ranged between 46 and 124% (median 88%). At the end of therapy the values ranged from 58 to 112% (median 80%). In 21 children comparison of data at the start and after cessation of bleomycin therapy was possible. In 14 children a decrease was noted (range 2–20%, median 9%); this was also statistically significant ($P < 0.05$). There were no clinical signs of pulmonary insufficiency.

DISCUSSION

T-cell malignancies often have a specific clinical presentation, i.e., lymphomatous features, especially mediastinal involvement, leukocyte counts >50,000 × 10^9/l, age >10 years, and CNS involvement at diagnosis [11]. On basis of this clinical presentation, a leukemia/lymphoma syndrome (LS) has been delineated [12]. In most studies, similar patients have been treated with high-risk ALL protocols and consequently reports include only a small number of T-cell malignancies. For example, 9 and 15% were reported by Pui et al. [1,4] and Steinherz et al. [11]. Due to differences between T-lymphoblasts and progenitor-B-blasts other treatment schedules can be considered. Main points of difference are: 1) the higher proliferation rate of T-lymphoblasts as a result a higher percentage of malignant cells is vulnerable to cell cycle-dependent chemotherapeutic drugs and consequently a more rapid reduction of malignant cell burden could be achieved [13]; 2) a shorter period between diagnosis and a relapse in T-cell malignancies (i.e., within the first 2 years) might indicate that more intensive treatment is needed [13,14]. The choice of chemotherapeutic agents as used in progenitor-B-ALL may also not be optimal for the treatment for T-lymphoblasts. Mice T-cell leukemia has been shown to be more sensitive to cyclophosphamide and cytosine-arabinoside vs. methotrexate and 6-mercaptopurine [15]. Also in vivo cyclophosphamide and cytarabine proved to be beneficial for T-ALL only [16]. However, these drugs are often relatively low dosed in these protocols. In addition, in vitro data indicate a lower expression of glucocorticoid receptors on T-lymphoblasts [17]. Also the prolonged use of drugs during the maintenance courses (especially methotrexate, 6-mercaptopurine, and in the Dana Farber Cancer Institute (DFCI) protocols prednisone) to which T-lymphoblasts may be relatively resistant can be a point of debate [17,18]. We developed an intensive but a relatively short (1-year duration) treatment scheme for all children presenting with a T-cell malignancy. Our treatment scheme has several points of which the profitable effect on lymphoblastic lymphoma has already been demonstrated: 1) combinations of a 4-drug regimen of vincristine, and anthracyclin, cyclophosphamide, prednisone, and methotrexate continuous infusion have evolved at the NCI from the original BACOP course [19]; 2) teniposide in combination with cytosine-arabinoside was described by Dahl et al. [20]; 3) the usefulness of cyclophosphamide and cytarabine was already indicated [16]. In addition, dexamethasone instead of prednisolone is known to reduce the incidence of meningeal leukemia [21,22].

In the present series, EFS was 72%. Comparisons with other reports for childhood NHL are hard to make as most authors consider their cases with T-cell malignancies with >25% blasts in the bone marrow as T-ALL and report them in their ALL studies. An outline of the often conflicting data is given in Table II. From the regimens based on Wollner et al.'s [23] LSA_2-L_2 regimen, only Patte et al. [8], Steinherz et al. [12], and Turbergen et al. [24] report EFSs >70%. In the reports of Steinherz et al. [12,25], EFSs >65% were attained in patients suffering from LS. Other studies with a favorable outcome are the schemes used in ALL from the Dana Farber Institute and the German Berlin-Frankfurt-Munster group and the treatment protocol for state III/IV lymphoma patients using teniposide and cytosine-arabinoside as described by Dahl et al. [20] and others [26,27]. These comparisons indicate that current protocols for ALL have similar results as our scheme in respect to EFS rates.

Analyzing the data of our patients, there was no significant difference in survival between the various stages, the presence of a mediastinal mass, age, initial leukocyte counts, and cytogenetic findings. With a larger patient sample it is possible that the difference in survival between low and high stages may become significant. The 5 CNS relapses are a major point of concern. Probably the prophylaxis using methotrexate might not be sufficient. An option, not supported by reports in the literature [7], is additional radiotherapy. This would, however, also mean that systemic methotrexate treatment has to be reduced to prevent a higher incidence of encephalopathy. We could not confirm that positivity for cell surface CD [2,4], CD4 [4], CD8 [4], and CD10 [2,28,29] or negativity for CD1 [2] was related to a better outcome; however, it should be stressed that the number of patients in our study is rather low. However, the value of a prog-

TABLE II. Major Reports on the Effect of Treatment of Pediatric T-Cell Malignancies*

Report	Selection[a]	Therapy	Patient numbers[b]	Survival	Therapy duration
Wollner et al., 1976 [23]	NHL	LSA_2-L_2	43	DFS: 76% (stI/II 100%, stIII 70%, stIV 63%, FU >25 m)	>2 y
Hvizdala et al., 1988 [7]	NHL	ACOP	50	DFS: 53% (stI/II 100%, stIII 54%, stIV 14%, FU 3 y)	>2 y
		LSA_2-L_2	35	DFS: 58% (stI/II 28%, stIII 93%, stIV 12%, FU 3 y)	>2 y
Katz et al., 1993 [33]	NHL	LSA_2-L_2	123	EFS: 56% (stIII 59%, stIV 48%, FU 5 y)	>2 y
Anderson et al., 1993 [34]	NHL (<25% BMB)	COMP	40	EFS: 35% (FU 5 y)	18 m
		LSA_2-L_2-mod.	124	EFS: 64% (FU 5 y)	18 m
Patte et al. 1992 [8]	NHL	LSA_2-L_2-mod.	84	EFS: 75% (stI/II 73%, stIII 79%, stIV <25% BMB 65%, stIV >25% BMB 77%, FU 57 m)	29 m
Sullivan et al., 1985 [6]	NHL (<25% BMB)	LSA_2-L_2-mod.	54	EFS: 55% (stI 100%, stII 67%, stIII 57%, stIV <25% BMB 39%, FU 3 y)	3 y
Dahl et al., 1985 [20]	NHL stIII/IV	SJCRH X-H	24	EFS: 73% (FU 4 y)	32 m
Tubergen et al. 1995 [24]	NHL (<25% BMB; 22% non-T-NHL)	LSA_2-L_2	281	EFS: 74% (FU 1.3–9.4 y)	>1.5 y
		ADCOMP		EFS: 64% (FU 1.3–9.3 y)	>1.5 y
Faletta et al., 1992 [35]	T-ALL	LSA_2-L_2	51	EFS: 40% (FU 3 y)	3 y
		T-cell2	36	EFS: 40% (FU 3 y)	3 y
		LSA_2-L_2-mod.	106	EFS: 40% (FU 3 y)	3 y
Shuster et al., 1990 [2]	T-ALL	LSA_2-L_2-mod.	235	EFS: 43% (FU 4 y)	3 y
Clavell et al., 1986 [37]	T-ALL	DFCI 81-01	39	EFS: 77% (FU 48 m)	2 y
Schorin et al., 1994 [26]	T-ALL	DFCI 85-01	20	EFS: 70% (FU 7 y)	2 y
Reiter et al., 1994 [27]	T-ALL	ALL-BFM 86	126	EFS: 73%, WBC >20 × 10^9/I 69% (FU 6 y)	2 y
Rivera et al., 1991 [36]	T-ALL	SJCRH XI	62	EFS: 48% (FU 4 y)	2 y
Pui et al., 1990 [4]	T-ALL	SJHRC X/XI	120	EFS: 46% (FU 5 y)	2 y
Steinherz et al., 1986 [12]	E-ros	LSA_2-L_2	13	EFS: 75% (FU 48 m)	2 y
Steinherz et al., 1996 [25]	LS	BFM-mod.	261	EFS: 67% (FU 6 y)	2 y
		New York reg.	163	EFS: 67% (FU 6 y)	2 y

*LS = ALL with lymphomatous features; FU = follow-up; m = months; y = years; EFS = event-free survival; DFS = disease-free survival; BMB = bone marrow blasts; mod. = modification; st = stage; E-ros = E-rosette positive.
[a]Patient category compatible with a T-cell malignancy as indicated in the paper and suitable for comparison.
[b]Number of patients as considered using the indicated selection.

nostic factor is strongly related to the effectiveness of the treatment and the cited reports have relatively low EFSs from 43 to 46% [2,4,29].

Concern has to be given to the toxicity of our childhood lymphoma regimens. Cardiotoxicity is one of the major impediments for further intensifying the treatment. The toxic effect of anthracyclines on the cardiac myocytes could be decreased by a cardioprotective compound like ICRF-187 [30] or the less cardiotoxic mitoxantrone instead of epirubicin [31].

The modified BACOP combination as used in our scheme includes bleomycin [19]. However, the efficacy of bleomycin in childhood T-cell lymphoma still has to be demonstrated. In our patients, the toxic effect of bleomycin was mild, probably due to its administration as a 6-h infusion instead of bolus injection. In the long term, infertility in the boys due to cyclophosphamide can be expected in several cases. Furthermore, the occurrence of secondary malignancies in relation to the use of epipodophylotoxins is important to consider.

Our study indicates that the differences between T-NHL and T-ALL are probably artificial. Also the cytogenetic changes, as found in our patients, have been reported for both T-NHL and ALL in general [10]. The majority of T-cell malignancies in children can uniformly be treated, whether or not the disease is localized in the bone marrow (T-ALL), mediastinum, or elsewhere (T-NHL). In conclusion, using this multidrug regimen the duration of treatment in childhood T-cell malignancies can be limited to 12 months in order to achieve results comparable with results in those reports mentioning the highest cure rates. Toxicity of this regimen is currently acceptable, but further efforts are needed to reduce the toxicity to heart, lungs, and gonads, and to prevent the development of second malignancies.

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